**Meeting Minutes**
**Scientific and Medical Accountability Standards Working Group**
**July 6, 2005**
**Grand Hyatt San Francisco**
**10AM-6PM**

**Attendance:**

*Working Group Members*

Alta Charo
Jose Cibelli
Kevin Eggan
Ann Kiessling
Robert Klein
Jeffrey Kordower
Sherry Lansing (co-Chair)
Bernard Lo
Theodore Peters
Francisco Prieto
Harriet Rabb (co-Chair)
Janet Rowley
Jeff Sheehy
Jonathan Shestack
Robert Taylor
James Willerson

*CIRM*

Zach Hall, Ph.D., CIRM Interim President
James Harrison, CIRM Counsel
Kate Shreve, CIRM staff
Nicole Pagano, CIRM staff
Jennifer Rosaia, CIRM staff

**[Welcome, Sherry Lansing]**

**[Introduction to the CIRM/Progress-to-Date, Zach Hall]**

Dr. Hall provided a contextual overview for the first meeting of the SMAS Working Group. Applications for Training Grants were received on July 1st and will be reviewed in August by the Grants Working Group. Before the CIRM is able to award grants, it must establish guidelines that will govern research carried out with grant funds.

[Roll call]

**Agenda Item #4: Role of the Scientific and Medical Accountability Standards Working Group [Zach Hall]**

**[See slide presentation]**

The functions of the Standards Working Group are set forth in Proposition 71 and include recommending to the ICOC:

- scientific, medical, and ethical standards,
- standards for medical, socioeconomic, and financial aspects of clinical trials and therapy delivery to patients,

- for oversight of funded research to ensure compliance with standards,
- for the rules and procedures to govern the Standards Working Group's operations

Per Proposition 71, the Standards Working Group will be asked to consider:

- Informed consent
- Controls on research involving human subjects
- Prohibition on compensation
- Assuring compliance with patient privacy laws
- Limitations on payment for cells; and
- Limits for obtaining cells

All Working Groups of the CIRM are exempt from California's Bagley-Keene open meeting law. However, the ICOC has decided consider making the meetings of the Standards Working Group open to the public. **Document:** *"Scientific and Medical Accountability Standards Working Group Proposed Meeting Procedures"* is included in the meeting materials.

The Standards Working Group will:

- Gather and analyze information;
- Reach decision points on proposed standards;
- Prepare draft and final recommendations to present to the ICOC;
- Give public notice of meetings in a timely manner;
- Post proposed meeting agendas;
- Hold public meetings at which members of the public may comment on draft findings and recommendations;
- Take public votes on decisions and recommendations to the ICOC;
- Post publicly the working group's final recommendation and minority and individual opinions to be forwarded to the ICOC on matters that emerge out of the foregoing process; and
- Meet in confidential session only if needed (e.g., to review a complaint regarding [an] investigator's or an institution's compliance with medical or ethical standards adopted by the ICOC with any final action to be taken in a public meeting.)

[Working Group Comment on the *Proposed Meeting Procedures*]

**Lansing:** We should conduct meetings in public, as we are doing today.

**Klein:** The open meeting format used by the National Academies is a good model for how open meetings could proceed. Note that the NAS format provides less access to the public than do the Proposed Procedures, as it has broader confidentiality and closed meeting provisions.

**[Motion #1]**

**Rabb:** Proposed amendment to the Proposed Meeting Procedures (second bullet) to explicitly state that no vote will be taken without opportunity for public comment.

**Motion made: Rabb**
**Motion seconded: Klein**
**Voice vote: Motion passes unanimously**

[Public Comment]

**Charles Halpern:** Comments about other provisions of the Proposed Meeting Procedures and additional proposed amendments to ensure openness in keeping with Proposition 59 and Bagley-Keene.

Suggested Changes

1. **Timeliness of posting the agenda**
   Working Group policy should be to post notice of the meetings 10 days in advance.

2. **Posting of public notice**
   Notices should be posted on the CIRM website.

3. **"a proposed agenda will be posted"**
   A final agenda should be published 10 days in advance. No subsequent changes should be made.

4. **Timeliness of posting supporting material for a noticed meeting**
   Any documents to be discussed at the meeting should be posted 10 days in advance so that public participation can be well informed.

**James Harrison** [CIRM Counsel]**:** The Proposed Meeting Procedures provide for a timely notice. A potential problem with a strict 10 day requirement is that the Working Group could potentially need to convene on an emergency basis. The Meeting Procedures should allow such meetings under certain circumstances.

**Alta Charo:** Regarding distribution of materials, an approach taken at many meetings is that materials may only be discussed if they are available for audience members to pick up and read. Such an approach, accompanied by intent to distribute materials in advance, would give the Working Group flexibility.

**Lansing:** A small staff, including Harrison, Halpern and some Working Group members, should examine items brought up by Halpern and make recommendations back to the group.

**Halpern:** The staff process should be an open one in which interested members of the public have an opportunity to participate.

**Lansing:** The Working Group has passed the Proposed Meeting Procedures as amended, with the understanding that these may be modified. A small staff will receive additional input from the public and the Working Group will determine whether further modifications should be made.

**Hall:** Proposal: Materials should be made available to the public at the same time that they are made available to Working Group members. [Would apply to changes made to the agenda as well as to supporting materials for the meeting]

**[Motion #2]**

**The committee will adopt the entire resolution [regarding the Proposed Meeting Procedures] as amended and receive public comment on further amendments**

**Motion made: Klein**
**Motion seconded: Lansing**
**Motion amended: Sheehy**
Any materials made available to the SMAS will be concurrently made available to the public
**Voice vote**
**Motion passes unanimously**

[California Administrative Procedure Act requirements]

**Presentation by James Harrison:** The Working Group must comply with the APA in drafting and recommending medical and ethical standards for the CIRM. The interim standards will remain in effect until the Working Group recommends and the ICOC adopts permanent standards.

<u>Interstate consistency and collaboration</u>

**Hall:** 1) Free exchange of materials in the scientific community is critical. 2) An advantage of the existence of a set of national standards as promulgated by the NAS is that these may serve as an umbrella set of standards for different states to adhere to. The aim of the CIRM should be to try to maintain high standards while also facilitating exchange, except in unreasonable cases.

<u>Scope of Duties of the Standards Working Group</u>

**Hall:** Two items mentioned in Prop 71, Intellectual Property and conflict of interest do not fall within the purview of the SMAS.

**Harrison:** Proposition 71 charges the SMAS with establishment of standards for "financial aspects" of clinical trials and therapy delivery. This is intended to encompass things like standards for compensating donors and research participants. Research patents do not fall within the jurisdiction of this group. The ICOC is required to adopt standards for royalties and may consult the SMAS about IP standards through a mechanism set up by the ICOC. No working group is currently assigned to consider of IP standards.

**Lansing:** We may choose to address IP issues when we get to them in the context of discussing the NAS Guidelines. The sense of the committee is that we should deal with these issues.

**Shestack:** This Working Group is an appropriate place to get recommendations from ethicists, scientists and advocates on the ethical implications of IP issues, resource creation, and cell line banking.

**Charo:** Questions of patent policy at the federal and institutional level require expertise that is not found on this Working Group. The issues have strong legal underpinnings, as well as economic and contractual underpinnings as a result of existing agreements. These issues may call for an outside committee.

**Kiessling:** Request for clarification of the distinct charges of the three CIRM Working Groups and areas of overlap between these groups.

**Harrison:** In addition to the Standards Working Group (already discussed):

- Grants Review Working Group – charged with developing criteria and standards for evaluation and award of grants and loans, as well as evaluating applications and making recommendations to the ICOC for funding of grants and loans.
- Facilities Working Group – charged with developing criteria and standards for evaluation and award of grants for construction of stem cell research facilities and for evaluating scientific merit of facilities applications in consultation with the Grants Working Group.

Potential Overlap: The major overlap regarding IP agreements, which will ultimately be part of the Grant Agreements, will be between the Facilities and Grants Review Working Groups, as the Grants Review Working Group will be considering the scientific merit of the Facilities applications.

**Rabb:** Discussion of the Administrative Procedure Act as it pertains to the activities of the SMAS WG; specific process and timeline for considering the NAS guidelines, adopted by the ICOC as interim standards on May 23rd, 2005.

**[Motion #3]** (Transcript page 65)

**Adoption of California Administrative Procedure Act process for considering and recommending permanent standards to the ICOC.**

**Rabb:** This is a procedure for how we manage the process of deliberation and public input.

Explanation of the need to comply with the APA.

**Harrison:** SMAS members are neither state officials nor state employees, and therefore are not governed by laws such as the state Political Reform Act. The SMAS is advisory in nature, therefore it is not required to comply with Bagley-Keene. However, the SMAS is advisory to a state agency, and that state agency is charged with adopting standards as regulations consistent with the Administrative Procedure Act. Therefore, we are trying to meld the process of this Working Group into the state law framework.

**Clarification of the motion.**
The SMAS WG will adopt the procedure [described by Co-Chair Rabb]

- The Working Group will receive public comment at this meeting as well as other public meetings of this Working Group-these comments will be transcribed
- Public comment will also be received on the CIRM website-this website will not be interactive
    - Staff will post a summary of the comments received to date so that the public is made aware of the direction the comments are taking
    - Ultimately all comments will come back to this working group and the public and will be the basis for considering recommendations to the ICOC.
    - Consistent with state law, the formal record will reflect all of the comments received
    - The CIRM will respond to all public comments
    - There will be two public hearings solely for the purpose of eliciting public comment

**Halpern:** The NAS Guidelines should be reviewed and modified to reflect recommendations of the SMAS Working Group. The NAS document, in some respects, does not function as a regulation. The raw material of the Guidelines needs to be turned into procedures. Certain provisions are also inconsistent with California law, e.g., the NAS requirement that no cells be harvested from an embryo older than 14 days old is inconsistent with the Prop 71 limit of 8 to 12 days.

Following additional discussion, the committee voted to adopt the process described above for considering the Guidelines.

**Motion made: Prieto**

**Motion seconded: Sheehy**
**No objections**
**Motion passes unanimously**

Discussion of NAS Guidelines

**Rabb:** The Guidelines can be divided informally into 4 categories
1) ESCROs;
2) review by boards other than ESCROs (IACUCs, IRBs);
3) Donation of tissue including tracking and review of research;
4) Formal or individual banking of cell lines

Two members of this Working Group were involved in the creation of the NAS Guidelines. They will briefly address topics that have generated significant discussion 1) oocyte donation (Rowley) and 2) chimeric research (Charo).

These issues are being discussed not only because they represent a personal interest but to illustrate that we are going to address the hard issues—there is nothing we cannot talk about here. The objective is not to talk about where we expect to end up, but where we start.

**Rowley:** NAS Guidelines were framed in the context of several critical considerations:

1) Generation and use of human embryos for research in this society is a contentious issue and it is essential that the process is treated ethically
2) Unlike many other countries, the US does not have, and urgently needs, national guidelines
3) Any guidelines must accommodate continual revision as this is a rapidly changing field.

The NAS committee accepted as a starting point two previous NAS reports that called for a) a ban on reproductive cloning, b) a resolution the hESC research should proceed as fast as possible

Oocyte donation and risk(s) to the donor (Please see transcript for full discussion.)

- The most serious risk to donors appears to be ovarian hyperstimulation syndrome (OHSS), resulting from use of natural or synthetic hormones to induce ovulation.
- Available data is inadequate

(Discussion of OHS Causes – please see transcript.)

Related ethical issues (outlined by Magnus and Cho in Science, June 17):

1) Problems of international collaboration in situations where ethical guidelines differ. Adoption of common rules by US institutions will facilitate sharing of cell lines and should be a goal.

2) Non-medical oocyte donation differs from sperm donation and should be compensated differently
3) Care should be taken not to oversell the technology (e.g., gene therapy legacy)

Donor Compensation
(Please see transcript for full discussion of donor compensation and number of donors needed.)

**Charo:** Prop 71 position on donor compensation was so strong that it drove the discussion within the NAS committee on this issue. Since Prop 71 was thought to be the driving force financially in the research, the only way to maximize interchangeability between states was to follow California's lead (by prohibiting compensation) I was under the impression that this particular issues was beyond discussion at this stage.

**Klein:** Proposition 71 does not permit compensation to egg donors, either directly or indirectly. There is a separate state law on the books that dealt with compensation and prohibited compensation in California. Reimbursement for out-of-pocket expenses is allowed.

**Eggan:** It does allow reimbursement.

**Klein**: Yes

**Charo:** Of out-of-pocket expenses. But not opportunity costs.

**Eggan:** Is that directly proscribed in the Proposition?

**Klein:** Yes.

**Kiessling:** This issue would become clearer if addressed in a more orderly way.

**Shestack**. What do people who know a lot about this issue anticipate in terms of the demand for donated oocytes in the interim period [before human oocytes are no longer needed] so we have a sense of how many people we are talking about [who would be affected]? Where do women come from who are donating eggs for research?

**Kiessling:** This is common. Women who have a family member [in need] There is no foreseeable limit to the number of women willing to help—no inducement is needed. I defer to Dr. **Cibelli** to supply projections on the number of women

[who may be affected]—the problem is we do not know how long it will take to replace the egg.

We don't understand the egg at a molecular level yet so cannot anticipate when it can be replicated in the lab. The more we invest in [research on] the creation of an artificial egg, either from existing cell lines or elsewhere, this will limit the number of women that we will have to ask to donate their eggs. Jose has a better sense of this.

**Cibelli:** Technically, if we take the Korean work at face value, so we can replicate what they've done, that means one woman per cell line. The immediate application is to understand disease not treat a patient.

Take, e.g., 10 different diseases, it would be nice to have 10 different cell lines from different patients who carry the disease. This would mean between 100 and 500 women.

The problem is the Korean study would be hard to replicate. They are ahead of us in terms of expertise and efficiency.

Given this factor, ~1000 women will be needed.

To be clear, we are talking about the NAS recommendation (3b) which states that a woman should be reimbursed only for direct expenses.

You will come to regret putting yourself in the position where you cannot reimburse for time and effort. This is very precious to the scientific community, sometimes you have to compensate for it. Not to say that it should be the incentive for oocytes, but we are going to need them. Speaking as a scientist, I would leave [the option of compensation] open.

**Lansing:** Women undergo this procedure all the time for infertility reasons. Those that are not used are destroyed, correct? These would be good eggs for [ESC] research?

**Cibelli:** This is complicated—the egg is not designed for the insult from IVF practices (needles, microscopes] or remaining viable outside of the human for long. For this research, you want the best materials—those that are leftover materials from IVF may not be the best materials to work with.

**Kiessling:** Dr. **Cibelli** is referring to eggs that fail to fertilize. Two government panels that have been convened charged with looking at this issue have not come to consensus on whether or not women going through IVF should donate eggs for research. Until we learn how to cryopresesrve eggs, there is time constraint issue. You cannot do an experiment with only 2-3 eggs—to burden a woman going through IVF with considering donating multiple eggs is a complex issue particularly with respect to the c**hall**enge of gaining true informed consent

**Lansing:** To be clear—there are not leftover eggs?

**Kiessling:** There are rarely "leftover eggs" unless you've got a program organized. There are some programs in England that always have patients to donate 2-3 eggs for research. The concept of leftover eggs is only if, for religious reasons, somebody will not cryopreserve embryos (to avoid risk of destroying embryos) then only a limited number of eggs are fertilized.
**Shestack:** You are not asking about fertilized eggs on a prospected basis—the donation as opposed to useful eggs?

**Kiessling:** No. Leftover eggs.

**Charo**: Ordinarily there is nothing left over from the products of IVF because every egg is potentially useful for fertility treatment. There is no such thing as a leftover egg unless a woman decides not to fertilize them all.

**Rowley:** That isn't so. [Sherman Elias] says he has freezers full of leftover oocytes. The point made [by **Cibelli** and **Eggan**] is that you want to start with the best material. We have no experience using frozen oocytes to try to do SCNT.

**Kiessling**: Frozen oocytes are not common. Some [programs] are effective.

**Rowley**: [Elias] has several thousand.

**Charo**: Aren't those failed to fertilize eggs? The egg was exposed to semen?

**Rowley**: Never exposed to semen, according to Elias.

**Lansing**: My question was whether this was a good source for us to access.

**Eggan**: My understanding is the oocyte freezing is still a difficult procedure, not well-established at IVF clinics. It is true that optimizing oocyte freezing is a very desirable thing to do. It would alleviate the constraints placed on this research and on women's reproductive health, in general. This is something that I would urge the institute to consider funding directly.
Scientists should consider the demand for oocytes and other alternatives, but need to operate a well under the assumption that these alternative may not come. We need to consider how to move forward within the functional framework that currently exists; the derivation of embryonic stem cell lines from started embryos and by nuclear transplantation as established by the South Koreans.
Regarding reimbursement: Prop 71 prohibits compensation but reimbursement reads directly in the language and can be broadly interpreted. We should discuss the flexibility allowed by this language. The UK example raises the question of whether women will donate [oocytes] in the absence of compensation. It is important to leave some flexibility in terms of defining

“reimbursement.” Finally, failed to fertilize [oocytes] are an undesirable source of material with respect to both the success of the research and the predicament placed on the clinician/IVF recipient.

**Lo**: [In acknowledgement of Sherry **Lansing**’s question-why don’t we use oocytes that aren’t needed]
With an IVF patient, you do not know whether you are going to need to use all of the oocytes retrieved [for reproductive] purposes and do not want to put the woman in a position of potentially regretting having donated a portion of her oocytes for research purposes.
While [**Rowley**] mentioned that one OB-GYN was able to use these oocytes for research but it remains unknown how successful it is [on a widespread basis] to effectively thaw oocytes—given their high intracellular water content, this process is difficult.

**Eggan**: To clarify: There are well-distributed methods to create the unfertilized egg for use for NT—but these are not well established. Once the oocyte is fertilized, and becomes an embryo, there are ultrastructural changes to the cell which allow them to be frozen. There are tens of thousands frozen *embryos* that are being stored for reproductive purposes which are a source of SC lines which are being used. These cannot be used for nuclear transfer. Only unfertilized oocytes would be usable for NT.

**Rowley**: To clarify: In quoting Sherman, the oocytes that are frozen may not be viable for NT—this question has not been answered.

**Lo**: [Question directed at Rob **Taylor** and the SWG Working Group] If we are going to proceed with SCNT for research purposes, the most feasible source of biological materials are fresh oocytes donated for the purposes of research. This has raised concerns.
Re: Short term risks:
Is the risk of hyperovulation related to the dosage of hormonal manipulation?
Does the effort to maximize the oocyte yield on the part of the clinician pose an increased risk? [Greater than 1%]
Are the charges of long term side effects valid? Eg., infertility of he donor due to octal depletion, ovarian cancer-what is the evidence of this association?

**Taylor**: The best population to avoid ovarian hyperstimulation syndrome would be an egg donor donating eggs for research purposes.
There is not a clear known linear dose-response effect but the greater the hormonal stimulation, the higher the estuarial level. Estuarial, along with other local ovarian factors, activate the Vega-F gene promoter. There are estrogen responsive elements on that gene—we have a level of understanding of how that gene is turned on. The more turned on [the gene] is, the greater the vascular permeability in severe OHS syndrome.

In a group of women who are not going to become pregnant, in whom you are not pushing the ovary so hard to get lots of embryos for reproductive purposes, you would be in a position the come up with clinical protocols which would limit the risk of [OHS syndrome].
Other risks, including twisting of the ovary an bleeding likely due to [repeated] punctures to the ovary, can be reduced by reducing the number of oocytes and follicles you stimulate and the amount of trauma to the ovary.
These risks can be more easily mitigated in women undergoing stimulation for egg donation for research purposes.
Regarding compensation: Based on personal experience, IRBs may not approve protocols that do not offer some sort of compensation to women undergoing egg donation to offset the risk these women are taking.
If [CIRM] regulations are too strict, this might limit the number of women who want tot volunteer but are not able to because of IRB restrictions.
In terms of long term risks: These are theoretical. Women are born with ~400,000 eggs of which they will, during a lifetime, ovulate 400. So there are many excess eggs. It is unlikely that we are depleting a [significant number] of those. There has been some recent literature that suggests, in animal models, that eggs might be replicating in the ovary after birth-something that we did not believe several years ago. Perhaps some of the hormonal medications [used to stimulate the ovaries and control the # of eggs produced] may have some effect on egg growth in women. In a mouse model, it has been shown that those drugs might reduce the total number of eggs in the ovary.
So trauma to the ovary [from the egg retrieval procedure] or hormonal medication may have effects on number of eggs within the ovary in the long term.
Regarding ovarian cancer—there is a clear association between long term infertility and an increase risk of ovarian cancer. Because women with long-term infertility have received a lot of infertility drugs, that association has been coupled but there isn't very strong epidemiologic or chemical mechanistic evidence to support that association.
This has not been determined. There are data on either side that suggests an increased risk but these data are on women who have received multiple episodes of ovarian stimulation. In this context, it is not a serious concern.

**Rowley**: California can try to follow the example of the S. Koreans and really develop these skills in America by:

(a) Developing technical training programs or
(b) Collaboration

We are paying a high price for our inefficiency.

Second, the American Society for Reproductive Medicine, June 30, 2005 [sent to **Rowley**, unknown publication source] has a two-page paper on complications of hyperstimulation. Cancer is discussed among the long-term complications. One report [Brinton] indicated that there might be an increase in breast and gynecological tumors—but there were few subjects in this study.

Ven et.al in Lancet 1999, concluded from a retrospective analysis of a cohort of 29,700 subjects that women has a transient but not overall increase in breast or uterine cancer. While there is a need for further monitoring, their conclusion is that it does not appear that ovarian, breast, and endometrial cancer are increased as a consequence of ovarian hyperstimulation.

**Prieto**: [Questions posed to Drs. **Taylor**/**Kiessling**] Does OHS ever occur in the absence of pregnancy? Regarding compensation: Isn't is reasonable to expect that institutions will include medical treatment for any and all complications of the medical procedures involved in oocyte donation as part of reimbursement?

**Eggan**: We are in the process of designing studies to replicate the work at Harvard and in long discussions with our own ESL oversight committee as well as our IB, it is clear that a form of insurance is going to be a critical component of this an that all oocyte donors [in my own and my IRBs opinion] should be insure an covered for the course of their participation in superovulation, oocyte donation, and retrieval process.

**Prieto**: So that is becoming standard—but does it include treatment for complications that may arise in the future?

**Eggan**: No-not in the long-term.

**Prieto**: If we are not able to provide compensation, [we may want to explore] another mechanism such as "enhanced reimbursement" , to make sure that women who donate don't put themselves at any risk or future jeopardy, particularly considering the current status of health insurance.

[James **Harrison** reads the text of the law that covers compensation-See Health & Safety Code 125290.35 (a) (3)]

**Harrison**: The area where the SWG has some latitude is in terms of defining what is covered as reimbursement for expenses and what expenses entails.

**[Break for lunch]**

**[Kiessling presents PowerPoint on oocyte donation. See transcript pages 118-126]**

**Key issues faced by Kiessling et.al and the Ethics Board in developing the first egg donor program for stem cell research.**

(a) Should this research be done?
    a. Conclusion: Yes, as long as guidelines for fully informed consent were followed and the donor was determined to be mentally and physically capable of egg donation

(b) Who should donate?
    a. Women between 21-34 with at least 1 biological child

(c) Should the donors compensated?
    a. Note: Local compensation is in place in almost every place in the country. The concern was would you get any eggs donated for research purposes if you didn't compensate donors? In actually the population that donates for research is different than that which donates for reproductive purposes.
        i. Conclusion: Women should be compensation for their time/travel/childcare.(Average of $4,000 for the entire multi—phase process)

(d) Recruitment-commitment to transparency
    a. Needs to be targeted to req'd audience-in this case, mothers.
    b. Evaluation of safety
        i. Psych screening/counseling
        ii. GYN/reproductive endocrinologist screening
        iii. Screening by "independent study monitor" to rule out coercion, determine donor's motives and understanding of procedure are appropriate

(e) Costs
    a. Paid for by a public not-for profit source-all financial transactions are for public consumption.

**Agenda Item #5: Consideration of the National Academy of Sciences Guidelines for Human Embryonic Stem Cell Research**

**[Alta Charo presents an overview on issues related to chimeric research]**

The NA committee's report focuses the first sustained attention on the "preclinical research phase" which involves lab and animal work. Certain aspects of this "translational" work are going to require that human materials be exposed to non-human materials to advance the science to human trials.
Definition: These are entities that have two different species' issues combined in some fashion—this is done routinely in the lab. For example,

- Pig valves are used as replacement heart valves in humans
- Human skin grafted onto mice

Taken out of context, the concept can be alarming—there is great potential for public misunderstanding which . As a result, there needs to be:

a) careful oversight in this area
b) clarity about what we know and o not know about this type of research

NA's reasons for chimeric research:

1) Basic research--To test the ability to differentiate human stem cells down the lineage of interest. The most effective method of doing this is in situ e.g., a chicken egg.
2) For use as a model to test safety/efficacy for potential human transplantation—e.g., if you grow tissue from hESCs that is intended for human transplantation, you would want to test its safety/efficacy in a non-human model first. Additionally, you would want to determine that the tissue being transplanted was made up of fully differentiated cells which could be tumorgenic. This allows you to test how undifferentiated cells as well as differentiated cell will react in vivo.
    a. This was identified as a primary area of focus by the FDA.

These are important preclinical research steps that seem to be the kind of steps that the FDA requires before moving into clinical trials.

Safety/ethical concerns of chimeric research:

- Any time human and non-human materials come into contact, there is a risk of viral mutation.
    - Existing oversight committees are a potential source of authority here such as the institutional biosafety committees
- Animal welfare (covered by Federal law, IACUCs)
- Careful attention should be paid to the stage of development of the animal into which stem cell derived tissue is implanted and the level of assuredness that the cells are fully differentiated considering the risk of random migration.

**NAs Recommendations:**

- Every time a researcher wants to put hESC derived tissue into a non-human animal, **regardless of the animal's stage of development**, he/she must consult a local institutional oversight board (ESCRO) which will assess the inherent risk of unintended consequences.

**NAs Recommendations for research that should be <u>prohibited.</u>**

- Putting hESCs into a non-human primate
- Prohibition on breeding chimeric animals

The NAs recommendations re: chimeric research supplement but do not replace existing federal guidelines.

**[end of Charo overview of NA recommendations re: chimeric research]**

**Peters**: How precise is the [NA reference] to chimeras?

Does it refer to a single cell that would have more than the normal number of chromosomes, some representing two species? Or to a single tissue

comprised of the cells of two different species? How is it distinguished from xenotransplantation?

**Charo**: The NA definition was, “an organism composed of cells derived from at least teo genetically different cell types. The cells could be from the same or separate species.
E.g., the example used describing altered DNA or additional chromosomes would not apply. This is about cell-cell combinations and not about intracellular changes.

**Peters**: Did questions that are more anthropological in nature come up in discussion such as definitions of human nature?
**Charo**: This came up with respect to two areas.

(1) animal welfare
(2) “species integrity”
    i. A mouse with human material likely does not have the architecture to substantially change its “mouseness”
    ii. With non-human primates, the architecture is more similar and raises complex questions of what the end result may be of coming similar tissue and architecture.

With respect to the larger [philosophical] question of the nature of this type of experimentation, a concept that is recognized in the field of biology [but not always in popular understanding about biology] which is that there is a degree of arbitrariness an antiquatedness about the taxonomy by which we define species...The closer you get to the question, the less clear it becomes and the harder it is to argue that there is something inherently wrong in breaking through boundaries that, in some ways, are not genuine boundaries.

**Rowley**: We thought that an ESCRO committee was very important because we thought that some of this depended on a) the scientific question being asked and b) was this the only way to answer it. There would be different considerations depending on the type of research/ therapeutic potential
E.g., for research involving injecting a few embryonic stem cells into an animal to differentiate it toward neuronal features or dopamine producing cells in an animal Parkinson’s model versus injecting a lot of cells to observe where they migrated in the brain which might raise more questions. The ESCRO and the investigator need to deal with these issues. If possible, one would appropriately try some of these experiments with primate cells and move to human cells if appropriate based on the results [of research with primate cells]

**Kordower**: A lot of reasons why people don’t use primates are they are difficult to get. The breeding of monkeys fro this purpose is a very difficult task-one which most places are not set up for.

**Prieto**: We do have a major primate center associated with the UC—these issues will come up. This center will submit research proposals.

**Kordower:** Whatever you find from primate to primate will have to be replicated in the human, it seems to be an appropriate step.

**Prieto**: The point was made that there are some things that we should initially try in other species

**Kordower**: I agree with that—I'm not sure that the primate is the right species.

**Charo**: This echoes the debate that was going on [with the NA committee]. This let's us reiterate Janet's point that the investigator who comes forward with an idea will be asked to discuss with the ESCRO why he needs to do [the research] in the way her wants to do it and are there alternatives?
These questions need to be case-specific—it is very hard to give fixed categories of research as opposed to having this conversational approach.

**Eggan**: The broader question for this group is to what extend does it want to micromanage these big issues and to what extent this group wants to put the power to make these decisions in institutional hands is an important question we should discuss.

An important proposition would be that this group demand that institutions which are involved in hESC research have an ES oversight committee.
We could recommend what the constituency of such a committee would be and how it should act and what its jurisdiction within that institution is.

**Klein**: Do you see a problem with having a joint ESCRO in the event a smaller institution cannot support its own ESCRO?

**Eggan**: As long as there was clear to whom [the smaller institution] was answering to and that they would be bound to the decision of that body.

**Rowley**: The determination of the Academy was that to have a single overarching ESCRO would be too unwieldy but that smaller institutions could rely on e.g., a regional ESCRO. WE do want the opportunity for there to be more conversation between the ESCRO and the investigator—if you were to have a regional model, you would want several sites in California.

**Eggan**: Almost every institution has its own unique internal issues. While there may be the desire to have broader scale oversight for smaller institutions It may be more effective to have institution-base ESCROS. The concern is that the farther you remove the oversight group from the institutions the more unwieldy it will be for the investigator.

**Rabb**: In case the public is not aware of the context of this conversation-- the ESCROS will be charged with reviewing individual hESC protocols to provide ethical oversight. Some considerations at the institutional level are:
Institutional independence
Capacity for distance

**Cibelli**: Would the ESCRO need to approve protocol before it is eligible for funding? Otherwise the ESCRO committee review would be an academic exercise without any power.

**Rowley**: The NA's vision is that the ESCRO review should be done early in the process to be sure that the science has some ethical and scientific merit to it, that it wasn't duplicative of other research being done.

**Charo**: In terms of enforcement, there are two mechanism or "teeth" that are anticipated.
One is institutional—by means of the regular mechanism for regulating the faculty—if faculty do not follow the established rules, then the institution sets its own disciplinary measures.
For funders, it is up to the funders whether they want to make review by an ESCRO a condition for funding.

**Cibelli**: This committee should make these determinations.

**Charo**: This committee could decide whether going to an ESCRO is a condition for receiving Prop 71 funding.

**Hall**: 1)I think institutions that submit grants to the CIRM should have an ESCRO or an affiliation with an ESCRO. This should be a condition [for funding].
2) The ESCRO committee should have signed off on the research protocol BEFORE we accept the application except under unusual circumstances. This speaks to the same tension one find with IRBs. Is there intent to ensure the protection of human subjects is in place versus judging the science? In the other sense it is our job at the CIRM to determine is this a good experiment, has it been well planned? How does it fit in? I think it will be judged at both levels both at the institutional and CIRM levels—there is [going to be] that tension always.

**Cibelli**: Money talks. If you can tie an ESCRO approval to the release of funds, that is the only way you can enforce it.

**Lansing**: If you are going to have local ESCROs, does that mean that people are going to be doing research in one part of the state that is not permitted in another part of the state?

**Charo**: It is still a question of whether or not ESCROs will be unique to each institution or whether institutions will band together to share one for the region or

one for all Prop 71 funded research. There are pros and cons (as introduced by Dr. **Eggan**] of centralized versus local levels of ESCRO review.

**Lansing**: The concern if ESCROs were regional—it may introduce unwanted variation and tension.

**Prieto**: The ESCRO would be a preliminary step. We would expect that a certain level of oversight would have happened at the institutional level (or within groups of institutions] There might be an advantage of having groups of institutions establishing an ESCRO—this might have the effect of insulating the ESCRO from institutional pressures.

**Cibelli**: We need to decide if ESCROs are a good idea for California and move on. What are the specific functions of the ESCRO?

**Charo**: The ESCRO is imagined as a generalize body that serves:

1) as a place to go if you want to derive new lines because you have to explain why the old lines are inadequate.
2) To do an ad hoc review of those lab experiments that raise special concerns (e.g., chimeras; identifiable cell lines)
3) As a source to build knowledge/experience in recognizing issues that have not been addressed to revise or extend existing standards
4) As a regulatory body which has the authority to reject prohibited research such as the use of new ES cells in a nonhuman blastocyst.
    a. It is not supposed to be there as a peer review committee looking at the value of the science independent of the specific question before them—the questions about scientific merit only come up when tied to the question of whether or not the experiment is justified.

It might also serve as a forum for further public discussion, debate, conferences.

**Rowley**: The ESCRO would also be the institution that would ensure that lines used for research that have been imported from the outside have been obtained ethically; i.e. with appropriate informed consent. Also, the ESCRO could serve as a registry for cell lines in an institution., those that were developed at the institution as well as imported. As more lines come from different sources with many different forms of consent, it will be extremely important that each institution, for its own protection, have these mechanisms in place.

**Klein**: 1) Institutions with the infrastructure to support their own IRB should be able to act on their own rather than within an aggregate regional structure so we don't encumber already highly competent, fully scoped institutional review processes

2. We need to be clear that we are adopting these guidelines prospectively because we certainly have cell lines that were derived potentially with compensation. Some of our standards may well be state-specific (e.g., with respect to the compensation issue) but that doesn't stop out researchers from using biological materials from other states, which is an issue we need to address.
3. And then there are standards and cultural differences between countries. What is our position with respect to material from India or Singapore or China or Korea where different standards may have been adopted? Will we respect their standards so that our researchers can benefits from theirs?

**Rowley**: We did define the functions of the IRB versus the ESCRO. The IRB would be the place within an institution which would review patient consent forms and make sure that all of the appropriate guidelines for deriving any experiment using gametes or cells or embryos was appropriately done.
The Academy did consider that different ESCROS are going to come to different answers on the same question and thought that it would be important to see if it was possible to develop a national oversight body where ESCRO members could raise these issues for larger discussion—the last thing we need is a vulcanization of research across the country.
In California, you could set up a forum where local ESCROS could bring issues to a larger group for discussion.

**Rabb**: One of the things you might be discussing is some sort of funding that would facilitate meetings if there are institutional ESCROs as opposed to regional or one statewide ESCRO that would facilitate meetings among ESCRO members for some period of time until there was a jurisprudence among ESCROs that everyone understood—so think about a funding agency for CIRM.

**Hall**: I think the CIRM can play a useful role in making sure that there are no barriers between ESCROs. The CIRM might also be a natural place to convene a collective meeting of local oversight committee members to discuss common problems and facilitate communication. Regarding the National Academy question and a national oversight committee, it seems that, for the moment, that the National Academy is the best place. Through that committee we hold what we do in California will be coordinated with the efforts of other states.

**Lo:** One way to look at the issues related to oversight is in terms of what are the functions we are supposed to fulfill. They are heterogeneous.
- Some are policy-what is institutional policy going to be.
- Some is record-keeping-of the registry
- Some is protocol-by protocol analysis of the tough issues.

Once I look at functions, I always look at the best person or group to carry out that function. It isn't clear that the same group should be the one doing all those different things.

We also need to think of the benefits and burden of the additional oversight that we create. What go we gain from it? What are the potential burdens in terms of cost, inconsistency?
Some overlap is useful, too much is stifling.
A lot of the questions such as “Do we really need this new cell line” “Is there an alternative to this research?” also require in-depth scientific review as well as ethical analysis.
There needs to be a mechanism for learning from the pooled experience of individual ESCROs. It would be important to get the chairs of ESCROs together to discuss cases but unlike court cases, IRBs are required to lay out their arguments for how they considered a protocol-I don’t know if ESCROs would be required to do this but it would be useful to define these expectations for how the ESCROs would be expected to operate and document a history of its deliberations for the benefit of other ESCROs, investigators, IRBs. Perhaps CIRM could play a role in that

**Cibelli**: I would argue that rather than require prior approval from an ESCRO, institutions should send the proposal [o CIRM] pending approval of the ESCRO.

**Rabb**: Akin to how the NIH deals with conflict of interest—you tell them you have a conflict, but you can’t spend the money until you’ve managed it.

**Lansing**: There is a need for an overall ESCRO for the state. There could be local ESCROs that implement the will of the overall ESCRO but I am terrified of inconsistency across the state. This would breed unhealthy competition between institutions. We are entering a new field and we need consistency. We can change our views as we go along but we need to start with an overall policy,

**Hall**: That is the job of this working group—to play exactly that role.

**Cibelli**: The question is whether we delegate to the local ESCROs or whether this is going to be the role of this committee.

**Lansing**: I think this should be the role of this group.

**Cibelli**: How many meetings a year are you thinking about?

**Kiessling**: I want to make the argument that California does not need an ESCRO. This guideline was put in [by the National Academies] to make up for deficits that are in the IRBs. This is reminiscent of the old recombinant DNA committees that used to exist when we didn’t understand recombinant DNA. But California has an Institute in place. Massachusetts is going to need an ESCRO because we don’t have an overarching body that is going to review these proposals. CIRM is that overarching body. I’m not sure that in California, that isn’t going to serve the purpose that the National Academy meant which was having some expertise in place having to do with stem cell—you’ve created that

entity. Those reviewing the grants themselves are going to be the ones qualified to serve this function.

**Lansing**: We'll have consistent rules. This group is going to come up with guidelines.

**Kiessling**: That doesn't replace the IRB. Whether or not the questions that you are asking about the stem cell specific part of the project, it seems to me that there will be expertise on your committee.

**Eggan**: This group could public minimal constraints—if institutions want to instill additional constraints than they should feel free to do that. This group would not have jurisdiction over those that operate outside of funding from CIRM.
We have the opportunity to impose that those institutions which want CIRM funding establish their own ESCROS and that those ESCROs will also then have jurisdiction within that institution over that funding, over that sponsored research, or research in general which is not funded through the CIRM. We have an opportunity to essentially set the regulatory status in California for all institutions that want to participate in the CIRM.
Why is thee a specific need for ESCROs?-I agree with this general concern. As a scientist, I am concerned about being over managed or being the subject of too much oversight or regulation. One reason I think it is important to have [an oversight body] that clearly issues surrounding the destruction of embryos are weighty ethical and moral issues. If review of this research were within the purview of a human subjects committee it may pose an inherent conflict that would result in disallowing this research if a human subject committee were to decide that a human preimplantation embryo was a human subject, By placing decisions related to this type of research in the hands of another body, it creates a new class of regulation and helps to clarify these concerns.

**Rabb**: Apart from the question of human subject protection when the embryo is the focus--considering the issue of consent could still be a question for the IRB since you look at consent by embryo and gamete donors to determine that those consents were appropriate.

**Eggan**: Absolutely.

**Charo**: The IRBs are creatures of federal law and regulation. The federal regulations are extremely clear that an embryo is not a human subject. Now the Bush Administration has an Advisory Committee and may change those regulations. But for now, the IRBs do not have discretion to decide whether an embryo is a human subject and that therefore all research with embryos falls under their jurisdiction. It is not permitted to them under federal regulation. They are supposed to look at the process by which live-born people re giving biological materials, including their embryos, for research purposes. The focus of attention is not on the "protection of the embryo" which presupposes the notion about

insurance on the embryo. Their focus is on adults—how we recruit them, advise them, how they release the materials-whether its eggs, sperm, or embryos—and includes issues of confidentiality. The resistance to IRB review of stem cell research is not because of turning an embryo into a human subject—it's because they have no business reviewing basic lb research that doesn't involve human subjects. To don't have the expertise or the legal jurisdiction. The ESCROs were suggested as a way to fill that gap. We don't usually regulate lab science unless it involves an animal or genetic engineering.
CIRM could create its own ESCRO which will function for all CIRM-funded research and institutions can decide to establish (or not) their own ESCROs—it would be a lot of work. One of the advantages of a local ESCRO system is that this group could establish core principles which would apply not only to California's institutions but in determining if South Korea's or Singapore's review system is substantially equivalent and therefore their lines could be freely accepted for CIRM-funded research.
You cold limit yourself to this core and then there would be some kind of embroidery at the level of implementation (subject to local interpretation)-or the CIRM could establish its own ESCRO "soup to nuts". This would be a tremendous commitment of resources.

**Lansing**: You're saying their would be inconsistency

**Charo**: There would be a core consistency, and then there would be some variation around the state which would, following Bernie's suggestion, shrink as people discuss with one another how to address issues that arise.

**Prieto**: Given the limitation on staff of the CIRM (50) per Prop 71, we want to set out the guidelines as a committee but may not want to commit the CIRM or the working group to the work of being the ESCRO as long as we can delegate the work and ensure that it is done according to the terms we set out. We don't want variation. This doesn't have to be individual institutions, it may be groups of institutions.

**Klein**: This is not just a cost-benefit analysis—we have an absolute cap of 4% general overhead, 3 % for research oversight. It's an absolute trade-off within the cap of functions and utility of functions that can be performed. If we have a core that provides statewide consistency, there may be a difference in interpretation of an institution's caliber there will still be consistency in the standards each institution will be held to with respect to CIRM-funded research.

**Shestack**: Can you "shop" for an ESCRO or are you bound to participate within your regional ESCRO?

**Hall**: You would have to apply to the institution for your ESCRO. As a note: Anything that is centralized rapidly becomes less responsive to individual investigators. To investigators the ability to have a local committee that is

accountable to the administration locally and responsive in terms of timeliness/consistency is very important.

**Lansing**: Consensus is moving towards: We will establish these broad rules, local institutions will implement them. There will be some variation but overall consistency. That would make me comfortable.

[clarification on the role of the ESCROs]

**Charo**: The ESCRO is designed to cover preclinical work. The ESCRO is in the in-between world. The IRB comes in at the beginning when you're collecting embryos, eggs, sperm, then the IRB goes away and the ESCRO stands there for laboratory animal phases along with animal care committees. And then when you are ready to go into human trials, the ESCRO goes away and the IRB comes back.

**[Debate on clarifying this issue of when the IRB becomes involved.]**

**Kiessling**: How are projects going to be funded? They're going to be reviewed by [the Grants Review Working Group] I don't see why you need a layer of peer review on top of that. California has an alternative compared to other states—it has fully qualified scientists that are going to review the project for everything that this ESCRO is going to review it for. If it doesn't pass muster at that level, it doesn't get funded. If you want to pass a guideline that covers all types of funding outside of CIRM funding then we have to discuss an ESCRO because other funding agencies may not have this expertise. To require the creation of an ESCRO around the state would be duplicative of that level of expertise and oversight.

**Rabb**: The question is whether we would expect the grants working group to determine what questions an investigator has to answer to ethically justify the work as well as scientifically provide a protocol that's worth funding.

**Kiessling**: That is why it is a duplication of effort. The NIH covers both a scientific merit and ethical review.

**Rabb**: This group would establish core guidelines which would become part of the grants working group review?

**Kiessling**: Or the grants group would incorporate the ESCRO concept as part of its review.

**Rabb**: Who will decide on the core principles that will ethically establish boundaries for California funding?

**Kiessling**:
Incorporating guidelines into the scope of scientific review is a separate discussion of whether to establish a separate committee(s). I am troubled by the fact that there is more structure in California than in any place else in the world. It is redundant.

**Eggan**: We have no jurisdiction over whether or not everyone in California should be subject to some ESCRO. We do have the ability to enforce institutional ESCROs on institutions who want CIRM funding. I see the ESCRO as a broad-based group who should be knowledgeable about the nature of all hESC research going on in that institution—it needs to be a group, there fore, that is involved in every step of the research.
While I understand that there may be time when the ESCRO is the only one making a decision on a particular issue because there will be types of research which involve ESCROs outside of the IRB. It seems that almost any IRB decision that was made concerning ES cell research should also be reviewed by an ESCRO. E.g., derivation of new lines would likely necessitate an IRB review for donation of gametes or embryos because the human subjects in question are the donors and need to be consented. This would also be within the purview of the ESCRO because it needs to be decided whether or not these are ethically reasonable and important experiments to do with respect to ES biology.

**Kiessling**: Would that be done by the grants group?

**Eggan**: No. As a scientist, I think it's important that every institution be able to answer to greater outside criticism to what's going to in their particular institution. As a scientist, I feel great protection that there is a group of thoughtful people that are not directly related to funding the research who have though deeply about these topics and could answer to outside critics.

[points raised by **Eggan** regarding institutional accountability echoed by Zach **Hall**]

**Hall**: One of the roles of the ESCRO is to know who is doing what in the institution. Judgment needs to be made locally according to the rules we set up. [Cited example of the process of special ethics panel that reviewed Irv Weissman's work at Stanford dealing with putting human stem cells into mice brains]

**Rowley**: We need to come to consensus on this issue. I fall in Kevin's camp—This was discussed by the Academy---the experience of the RAC serves as an example of an effective another layer of review that served scientists well for an area that was very sensitive. hESC research is such a sensitive area that we should bend over backwards to show that we are doing this in a responsible fashion. I'm continually confronted on the President's Council with scientists who want no restraints

**Kiessling**: Kevin and I will tell you that's not true

**Rowley**: That is not the perception of a certain portion of the population and ESCROs offer a protection against that portion.

**Kiessling**: What happened to recombinant DNA review?

**Rowley**: There is a RAC committee at NIH which is now looking at gene therapy. Any proposal dealing with gene therapy is reviewed by this committee.

**Kiessling**: Not local committees any longer

**Eggan**: All recombinant DNA research is reviewed by a local biosafety committee.

**Lo:** The RAC offers some interesting historical analogies. Its role has changed over time. It started around the time concerns about recombinant DNA [began to be raised]; its role has really changed over time—particularly after the Jesse Gelsinger case. All gene transfer protocols in humans that are either funded by NIH or were an NIH-funded institution that derived the vector that's being used in the trial have to be reviewed by the RAC in addition to local IRB and local biosafety review committees. It is voluntary for people with completely private funding. There have been concerns that this delays the process., that it's not responsive to the timetable that protocol developers are on. Having sat on the RAC, I think it gives a level of review, both scientific and [sort of] ethics, that is not available locally. The difference between the RAC protocols and the CIRM protocols is that the RAC protocols often did not undergo NIH-type peer review-these would be from private or industry funding sources ( which the CIRM protocols would) for scientific merit. So often, many of the concerns raised are scientific questions—a lot of the concerns that are raised have to do with suggestions to try and reduce the risks to participants receiving gene transfer. Theirs is always the concern of whether this is worth the time and effort. Part of that was driven by the public concern about the adequacy of both the scientific and ethical review.
One of the goals of the RAC is to increase public trust (investigators may feel it to be a burden)

**Kiessling**: So this would be particularly valuable if there was no level of peer review.

**Lo:** It depends on whose perspective. From the scientists on the committee, it's an opportunity to engage in in-depth discussion.

Kordower: [Re: his own experience with the RAC] I did not think the process was that helpful and felt it did significantly delay our chance of going into the clinic. Other investigators I know felt it delayed them significantly and delayed bringing in FDA-approved protocol to the clinic.
From an academic point of view it was rigorous investigative day—in terms of bringing novel therapies to the clinic, we found it to be counterproductive.

**Prieto**: I come down in support of local ESCROs (at institutions or groups of institutions) The CIRM may have a process in place to perform this function ourselves, this will possible be the preeminent funding source for much of this research in California, but it will not be the only one. It does provide protection for the institution and the researcher and to be able to build confidence among the public that we have reviewed this [research] at several levels.
We could put in a stipulation for timely review.

**Sheehy**: How is this process going to help the ICOC fulfill its function. This is a new regulatory step but the ICOC still has overall regulatory responsibility. Are we abdicating responsibility for making decisions on ethical issues to local committees. I don't know if we have the authority to do that, by statute.

The ESCROs are a good idea given that we are not the right regulatory agency to oversee stem cell research in California—but before we approve a grant, we should know that it fulfills our ethical and scientific conditions for funding—that would be part of an ESCRO review. We would not want to delay research that may affect the lives of patients waiting for an ESCRO review. It is unclear how the ESCROs fit within the context of out processes—how do we ensure enforcement of the CIRM policies?

**[Public comment]**

**Don Reed:** Advocated for multi-stage consent process (British model) and reimbursement for time as well as public education effort ( in schools) to educate people about SC research and the work of the CIRM.

**Jesse Reynolds:** Concerned that the informed consent practice used to consent women donating eggs for reproductive purposes not be the same as that used to consent women donating eggs for research purposes.
The issue of who would bear the cost of short versus long term health consequences should be seriously considered. Some form of financial trust or long-term insurance program should be considered. There needs to be a requirement that the doctor/clinician administering the informed consent be a step removed from the research itself in order to avoid any potential conflict.
With regard to the ESCROs, there needs to be a layer [of oversight] where there is real authority that is independent. There are issues both with local IRBs and centralized bodies-it is unclear what the middle ground is but there is a necessity to have something with "teeth."

**Charles Halpern:** The NAS Guidelines re: the issue of ESCROs is not ready to come to a vote becomes it remains ill-defined and warrants further discussion of the committee to set “principles and standards”. The NA Guidelines e.g., do not deal with the question of a centralized body or the reporting structure for such as structure. Agrees with **Lansing** that a lack of uniformity in the state would undermine the public confidence in this process. The question of how the issue of oversight will be dealt with for private corporations needs to be dealt with.
In addition to having individual or group ESCROs, there should also be a provision that decisions made by an ESCRO must be reported centrally to the SWG and the CIRM and any approvals of chimeric research ought to be described in detail to this group which should sign off before research proceeds. It should also be clear that when an institution takes CIRM money, they are committing themselves and all of their stem cell activities to follow the standards established by the CIRM.

**Prieto**: Ultimately the ICOC bears the full responsibility. I do not think we can enforce our standards on behalf of other funders., but we would be looking at that if people were ignoring them.
Each institutions or group of institutions should have an ESCRO will allow for flexibility [for smaller institutions]
In response to Halpern’s stipulation that the committee should include public representatives along with individuals with diverse expertise. Within a private institution, by definition, they would need to go outside themselves for this expertise.

**[Break]**

[Presentation by Harriet **Rabb** recommending that the committee recommend to the ICOC that CIRM Staff (assisted by counsel) draft the guidelines into regulatory language that is consistent with California law. The aim is to increase the clarity of the guidelines as a working document. The guidelines would not be changed in the content or spirit in which they were written during this process. This will modify the rulemaking timeline and the timing of public comment proposed by Harriet at the start of this meeting.]

**[Revised Process as presented by James Harrison]**

The Working Group will adopt a motion asking the ICOC to direct the Working Group to develop precise regulatory language to for proposal to the ICOC to adopt as interim standards

The ICOC will consider the revised language and adopt it

A formal APA rulemaking period will follow

Thus there are two levels of public comment envisioned by this revised process—one associated with the development of precise regulatory language and a formal public comment period associated with the rulemaking process under the Administrative Procedure Act.

**Rabb**: [In response to **Peters**' question] The redrafting will apply to all of the NA guidelines.

**Peters**: Doesn't this amount to added/redundant work for this committee if the ICOC has adopted these guidelines as interim? Given that this committee will go through each aspect of the guidelines and could address regulatory language piece by piece.

**Hall**: This revised schema has the added advantage that it follows the design of Prop 71 that the Working Group should make recommendations to the ICOC on standards.

**Harrison**: Staff will revise the NA Guidelines into regulatory language as required by the law—the charge of this Working Group will not change in terms of considering the substance of the guidelines and whether or not modifications should be recommended to the ICOC.

**Eggan**: This would be formally enacting from our perspective that this is a reasonable starting place—once put in regulatory language it will be an easier baseline from which to proceed. Again, I would say that there may be no final rules—this is a changing field which may require constant revisions to these guidelines.

**[Public comment]**

**Halpern:** Commends the process and suggests approach to adapting the guidelines. He subject of banking and distribution does not lend itself so easily to regulatory language. The language needs to be changed to be consistent with CA law (e.g., 14 day versus 8-12 day limitation on harvesting cells)

**Auriti:** What is the intent of the committee with respect to use of pre-existing cell lines?

**Klein**: The Guidelines were adopted with a preamble that specified that it was prospective only. Additionally, I believe the adoption included an amendment that made the Guidelines consistent with Prop 71 in terms of a threshold of 8-12 as opposed to 14 days. Those points would be incorporated in the language that is to be adopted. These clarifying changes into regulatory language, as suggested, should be straight forward. The question of banking is an evolving topic that has not been settled nationally or internationally and should be discussed.

**[Public comment]**

**Reed:** This clarification is a necessary step.

**Motion: Harriet Rabb**
Recommendation to the ICOC that the ICOC direct the Working Group to propose specific language and recommend any changes that are necessary to conform the regulation as proposed to the law of the state of California to the ICOC at its meeting in September. The formal rulemaking process will commence after the ICOC has adopted those interim Guidelines, henceforward considered CIRM Interim Guidelines

**Motion Seconded: Robert Klein**
**All in favor. Motion passes**

**[Question raised as to when to address the issue of banking.]**

**Rowley**: The banking recommendation was drafted based on the UK banking guidelines. This was written to ensure that all the issues raised in the UK forms are addressed:
Having a central tissue bank
Should cell lines be accepted from other sources
How to treat distribution

**Klein**: These can be converted to regulatory language. “Institutions engaged in hESC research s**hall** seek mechanism….”

**Lo:** It may be helpful to look at the Guidelines and highlight areas that were taken directly from the NA Guidelines that clearly need to be revised.

**Charo**: In response to the question on the NAS intention on existing lines. Regardless of what their intentions are or are not, the actions of the ICOC supersede. Once a report is completed, nobody is allowed to speak for the committee. It’s the text [that speaks]. The text is silent on this point which means that people who want to adopt these recommendations are free to adopt them with or without retroactive application.

**Lo:** [Proposal to identify issues to frame the work of this Working Group moving forward. ]

**[Issue identification]**

**Peters**:

- What are research priorities for CIRM funding (is there an effort to minimize duplicative research and emphasize novel protocols?)
- Chimeric research-what is ongoing research in California

**Lo:**

- Banking and Stem Cell Registries
- Informed consent process for donors
- Payment to donors under Prop 71 and compensation for injuries suffered by donors as a result of participating in research
- "grandfathering" of existing cell lines
- International collaboration

[**Rabb**: it is not clear how to quantify or treat "injuries suffered" or identify the kind of services required to compensate an individual, insurance etc., Option related to this issue need to be carefully explored.]

**Shestack**: The question is mired in controversy. There is the federal example of the vaccine compensation trust fund-which is funded by contributions by manufacturers and consumers.

**Rabb**: The vaccine comp program does pay out which raises the question of whether the CIRM would want to create and comp model more like a worker's comp rather than injury liability model.

**Charo**: Establishing direct association and causality in research participants is a c**hall**enge. These models being discussed have all been carefully examined as systemic solutions. Creating a compensation scheme around this research area of egg donation would not be wise. You really want to focus round compensation for injury.

**Rabb**: We need to start by researching these topics rather than think about jumping into starting a program

[Topics continued]

**Eggan**

- Recommending sources of oocytes for NT (e.g., failed to fertilize oocytes)
  - What can be done, what should be supported in the long term?

**Cibelli**

- In creating disease specific lines, how to treat the ethical issues surrounding obtaining cells from sick children who may not reach adulthood to the point where they can decide whether they want to donate their somatic cells or not

    - **Eggan** amendment: How to treat all individuals unable to give true informed consent
  - What is the diversity represented in the existing cell lines

**Rabb**: We need to categorically consider the issues addressed by the NA Guidelines (Oversight, Donor Recruitment and consent, Banking etc.,) and need to come to conclusion over time as to how to deal with redundancy between ESCROS, IRBs IACUC where is this healthy and productive redundancy and where is it hindering? With respect to the discussion of donation, we have not addressed the problems that is inherent in the NA recommendation requiring consent at the time of donation for sperm donors. We need to consider whether sperm and egg donation should be treated differently.
With respect to Banking. What are the obligations of those institutions deriving and distributing their own lines?

**Shestack**: The question is whether or not the CIRM wants to set strong obligations for anyone that funds on release of biomaterials, data, and perhaps, cell lines that go into the general pool—whether that is a condition for funding

**Rabb**: Yes. Repository questions, in general.

**Shestack**: The committee may wish to address from a strategic point of view the relative potential that scientists consider between SCNT that requires oocyte donation and the use of excess fertilized embryos scheduled to be discarded.

**Eggan**: Provides example of the value of creating disease-specific lines. Specifically the fact that, given the complexity of gene interactions that result in certain disease phenotypes, it impossible to engineer a cell line or an animal to model these diseases. The only way we know that the genes are together in the right place to cause disease is when a patient manifests the [disease] phenotype. SCNT offers us an opportunity to capture that genotype and turn it into a model. It would be impossible to say a prior that an embryo or any cell line had the proper genotype to manifest disease. By taking skin cells from a patient that has the disease, we know that the genes that are required to cause that disease are present. We can make the ES cell line and now have an inexhaustible source of material of the genotype to differentiate into the affected cell type and observe the development of that disease.

**Taylor**: The ability to track donors ad infinitum to follow up on their health status is not addressed by the NA Guidelines. The ethical issues surrounding this are huge,

**Rowley**: The UK and EU require that all donors be trackable. This was implied in the NA banking recommendations but was never spelled out as to how to carry this out. The intent in the UK was to have the ability to report to the donor any discoveries using their cell lines that may have genetic implications for the donor.

But the question of what do if donors are found to develop disease—what are the reporting tracking/requirements is an important issue.

**Charo**: The FDA already required tracking for donor tissue transplant.

**Eggan**: HIPAA speaks to how this would be administrated.

**Charo** With respect to medical records/

**Shestack:** This becomes part of your initial screening and consent process.

**Taylor:** Couples/individual could consent to certain procedures which would determine how the cells get used. Everyone might not wish to agree to the same.

**[Strategy developed to deal with information gathering before the next meeting on August 30.]**

**[Discussion of Working Group strategy for August 30]**

**Hall**: Our first responsibility on the 30th is to consider the redrafted language. We will have some time to consider fully areas that addressed or not addressed by these CIRM Guidelines throughout the drafting period and APA process.

**Charo:** [proposal of alternated approach] to organize the comments around the issues addressed by the NA Guidelines and determine where the language is appropriate as written or deficient for CIRM purposes. For each area, we would develop lists of things we need to come to conclusion on that we don't have. Based on these lists, we could identify areas that require further research. This will focus the discussion. We do not want to duplicate the work of prior reports (HIPAA, NAS, Singapore] and become a report writing committee as opposed to one that looks carefully at the current language and identify areas that need to be tweaked in order to be implemented.

**[Development of information-gathering study groups]**
The Working members will be divided into study groups based on the framework provided by the NA Guidelines. These are Oversight Mechanisms; Donor Recruitment and Protection; Pre-clinical Research Standards; Banking; and Interstate and International Collaborations. These study group assignments will be made by the Co-Chairs and Zach **Hall** based on expertise, individual requests. The goal of this strategy is to divide the work of information gathering with respect to each category of interest and report back to group with respect to how the issue is addressed in the NA Guidelines, issues/priorities the working group should focus on with respect to the issue, and a proposal for how the working group should address priorities moving forward.

These smaller study groups would not come to individual “conclusions” but present the information they have gathered for the benefit of the full committee to serve as a platform for discussion at the August 30 meeting.

**[Public comment]**

**Reed:** This committee should produce statement on the ethical “rightness” of this research

**[Meeting adjourned: 18:18]**